is not hydrogen" is added to exclude subject matter of the non-elected G3 of the Restriction Requirement. Similarly, the amendment to R_6 is made to exclude the subject matter of the non-elected G1 of the Restriction Requirement. Thus, the amendments are made in response to the Restriction Requirement, not for patentability purposes.

Objections to the Specification, Claims and Abstract

The specification was objected to for lacking section headings. Applicants submit that the insertion of such headings, e.g. Brief Description of the Drawings and Detailed Description of the Invention, has rendered the objection moot.

Tables 2 and 4 were objected to as not very legible. Clean substitute copies of Tables 2 and 4 have now been provided.

The Specification was also objected to for lacking an Abstract. An Abstract has now been provided.

Withdrawal of the objections is requested.

Rejection under 35 USC §112, first paragraph

Claim 9 was rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse the rejection.

The Office Action took a position that a pharmaceutical composition for treating cancer was not enabled by the *in vitro* data which shows growth inhibition of carcinoma cells and of leukemia cells. Applicants respectfully disagree. The rejection essentially

means that the Office Action requires *in vivo* data for the enablement of the treatment of cancer. However, it has been held in court that *in vitro* data were sufficient to enable an invention for the treatment of cancer. See *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Applicants submit that sufficient information has been disclosed in the specification for a person skilled in the art to make and use the claimed composition of the invention. Withdrawal of the rejection is requested.

Rejection of Claim 1 under 35 U.S.C. § 102

A. Claim 1 was rejected under 35 U.S.C. § 102(e) as being anticipated by Bogden (U.S. Patent No. 5,736,517). The Office Action asserts that Bogden teaches numerous peptides (e.g. col. 4, line 57+) containing tryptophan for treating cancer. The Office Action takes a position that the tryptophan-containing peptides of Bogden anticipate claim 1 when the substituent variables of claim 1 are as follows:

n	is	0,
R_1	is	H,
R_{73}	is	H,
R_6	is	H,
R_2	is	substituted alkyl,
R_{72}	is	H,
R_{70}	is	H,
R_{71}	is	substituted alkyl,
R_{74}	is	H,
R_3	is	H or substituted alkyl,
R_7	is	H, and
R_{75}	is	substituted alkyl.

However, the Office Action erroneously states that Bogden anticipates claim 1 when the substituent variables are as listed above (wherein R_{71} in claim 1 is substituted

alkyl). Actually, the tryptophan-containing peptides of Bogden coincide with some of the compounds of formula I of the application only when R_{71} in claim 1 is H, not substituted alkyl. The compounds of formula I contain an indole moiety of tryptophan only when R_{70} and R_{71} are both hydrogen. But the compounds of formula I wherein R_{70} and R_{71} are both hydrogen were not elected in response to the Restriction Requirement. Thus, Bogden fails to anticipate claim 1.

B. Claim 1 was rejected under 35 U.S.C. § 102(a) as being anticipated by Crews (*J. Org. Chem.* 59, 2932, 1994). Applicants respectfully traverse the rejection.

Crews discloses the compound designated milnamide A. This corresponds to a compound of formula I as follows:

R_6 is a methine group bonded to the indole group, forming a 6-membered ring;

R_1 is methyl; and

R_{75} is -CH(iPr)-CH=CH(Me)-COOH.

When R_6 is bonded to the indole group forming a 6-membered ring, the compound of formula I is tricyclic. But tricyclic compounds involving the indole group were non-elected subject matter. Thus, Crews fails to anticipate claim 1.

Rejection of Claim 1 under 35 U.S.C. § 103

Claim 1 was rejected as obvious over Kashman (U.S. Patent No. 5,661,175) because Kashman teaches that hemiasterlin is useful as an anti-cancer compound. Applicants respectfully traverse the rejection.

A Rule 131 Declaration that was filed in the parent application is herein provided to predate Kashman. Withdrawal of the rejection is requested.

Conclusion

In view of the amendment and the above reasoning, applicants submit that the application is in a condition for allowance. A Notice of Allowance is believed in order.

In the event that the filing of this paper is not deemed timely, applicants petition for an appropriate extension of time. Any petition fee for the extension of time and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 01-2300.

Respectfully submitted,

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Enclosures: Abstract
Marked-Up Version of Amended Claims
Table 2 and Table 4
Copies of Executed Rule 131 Declaration

KLW:elp

APPENDIX

Pursuant to 37 CFR 1.121, a marked up version of the amendment is presented.

In the Specification:

In page 1, replace the paragraph beginning in line 5 (based on the line numbering presented in the left margin) with the following paragraph.

Summary of the Invention

This invention relates to novel biologically active compounds and compositions, their use and derivation.

In page 3, replace the paragraph beginning in line 19 with the following paragraphs.

Brief Description of the Drawings

Fig. 1 shows a comparison of antimitotic activity of Hemiasterlins with that of known antimitotic agents.

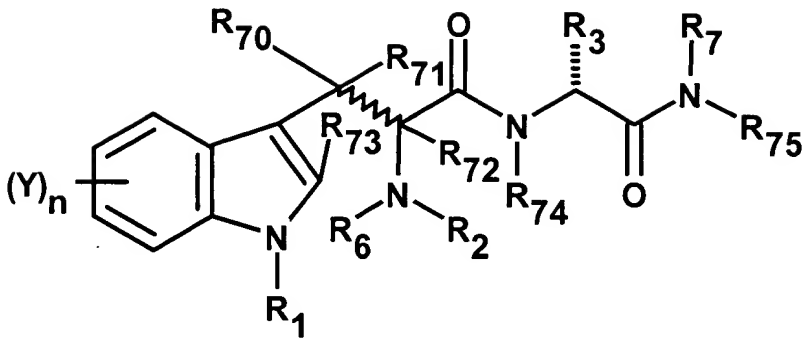
Fig. 2 shows the antimitotic activity of chemically modified Hemiasterlins.

Detailed Description of the Invention

Preferably, [R^1] R_1 represents a hydrogen atom or an alkyl group, especially a methyl group. More preferably, R_1 represents a hydrogen atom.

In the Claims:

1. (Twice Amended) A compound of general formula I



I

wherein:

R_1 and R_{70} independently represent a hydrogen atom or an optionally substituted alkyl or acyl group with the proviso that when R_{71} is hydrogen as hereinafter described, R_{70} is not hydrogen;

R_2 represents a hydrogen atom or an optionally substituted alkyl or acyl group or is absent when R_6 represents a group -CH= as hereinafter described;

R_{73} represents a hydrogen atom or an optional substituent or is absent when R_6 represents a methylene group or a group -CH= as hereinafter described;

Y represents an optional substituent;

n represents 0, 1, 2, 3, or 4;

R_3 represents a hydrogen atom, or an optionally substituted alkyl group;

R_{74} represents a hydrogen atom, a hydroxy group or an optionally substituted alkyl or acyl group;

R_7 represents a hydrogen atom or an alkyl group;

R_{75} represents an optionally substituted alkyl group or -Q'-C(O)X, wherein Q' is an optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH=CH-$, $-CH_2C\equiv C-$ or

phenylene, X is $-OR_8$, $-SR_8$, or $-NR_9R_{10}$, and R_8, R_9 and R_{10} independently represent a hydrogen atom or an optionally substituted alkyl group; and

i) R_6 and R_{71} independently represent a hydrogen atom or an optionally substituted alkyl or acyl group; and R_{72} represents a hydrogen atom; or

ii) [R_{71}] $\underline{R_6}$ represents a hydrogen atom or an optionally substituted alkyl or acyl group and [R_{72} represents a hydrogen atom or] R_{71} and R_{72} are joined together such that a double bond is formed between the carbon atoms to which they are attached; [and

R_6 represents an optionally substituted methylene group bonded to the indole moiety thereby forming a tricyclic moiety; or

R_6 represents an optionally substituted group -CH= bonded to the indole moiety thereby to form an aromatic tricyclic moiety;]

with the proviso that when

R_6, R_7, R_{70} and R_{71} are methyl;

R_2, R_{72}, R_{73} and R_{74} are hydrogen;

R_3 is t-butyl;

R_{75} is $-CH(CH(CH_3)_2)C(H)=C(CH_3)COOH$; and

n is 0, R_1 is not methyl.

2. (Twice Amended) A compound of general formula I described in claim 1, wherein

R_1 represents a hydrogen atom;

R_2 represents a hydrogen atom, or an alkyl group, or an acyl group;

R_3 represents a hydrogen atom, or an optionally substituted alkyl group;

n represents 0;

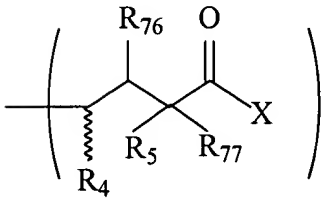
R_{70} and R_{71} independently represent a hydrogen atom or optionally substituted alkyl group;

R_{72}, R_{73} and R_{74} represent hydrogen atoms;

R_7 represents a hydrogen atom or an alkyl group;

R_6 represents a hydrogen atom, or an optionally substituted alkyl group[, or a methylene group bonded to the indole moiety thereby to form a tricyclic moiety];

R_{75} represents a group of general formula III,



III,

wherein R_4 represents a hydrogen atom, or an optionally substituted alkyl group; R_5 represents a hydrogen atom or an alkyl group; R_{76} and R_{77} each represent a hydrogen atom or R_{76} and R_{77} are joined so that a C=C bond is formed between the carbon atoms to which R_{76} and R_{77} are attached; and X represents a group $-OR_8$ or a group $-NR_9R_{10}$, wherein R_8, R_9 and R_{10} independently represent a hydrogen atom or an optionally substituted alkyl group.

3. (Twice Amended) A compound of general formula I described in claim 1, wherein

R_1 represents a hydrogen atom or an alkyl group;

R_2 represents an acyl group;

R_3 represents a hydrogen atom, or an optionally substituted alkyl group;

n represents 0;

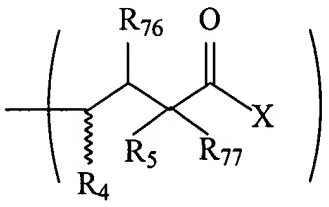
R_{70} and R_{71} independently represent a hydrogen atom or optionally substituted alkyl group;

R_{72}, R_{73} and R_{74} represent hydrogen atoms;

R_7 represents a hydrogen atom or an alkyl group;

R_6 represents a hydrogen atom, or an optionally substituted alkyl group[, or a methylene group bonded to the indole moiety thereby to form a tricyclic moiety];

R_{75} represents a group of general formula III,



III,

wherein R_4 represents a hydrogen atom, or an optionally substituted alkyl group; R_5 represents a hydrogen atom or an alkyl group; R_{76} and R_{77} each represent a hydrogen atom or R_{76} and R_{77} are joined so that a C=C bond is formed between the carbon atoms to which R_{76} and R_{77} are attached; and X represents a group $-OR_8$ or a group $-NR_9R_{10}$, wherein R_8, R_9 and R_{10} independently represent a hydrogen atom or an optionally substituted alkyl group.

4. (Twice Amended) A compound of general formula I described in claim 1, wherein

R_1 represents a hydrogen atom or an alkyl group;

R_2 represents a hydrogen atom, or an alkyl group, or an acyl group;

R_3 represents a hydrogen atom, or an optionally substituted alkyl group;

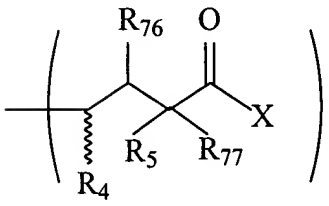
n represents 0;

R_{70} and R_{71} independently represent a hydrogen atom or optionally substituted alkyl group;

R_{72}, R_{73} and R_{74} represent hydrogen atoms;

R_6 represents a hydrogen atom, or an optionally substituted alkyl group[, or a methylene group bonded to the indole moiety thereby to form a tricyclic moiety];

R_{75} represents a group of general formula III,



III,

wherein R_4 represents a hydrogen atom, or an optionally substituted alkyl group; R_5 represents a hydrogen atom or an alkyl group; R_{76} and R_{77} each represent a hydrogen atom or R_{76} and R_{77} are joined so that a C=C bond is formed between the carbon atoms to which R_{76} and R_{77} are attached; and X represents a group $-OR_8$ or a group $-NR_9R_{10}$,

wherein R_9 and R_{10} independently represent a hydrogen atom or an optionally substituted alkyl group.

Table 2
NMR Data for the Hemiasterlins, Compounds 2, 3 and A. Recorded in DMSO-d_6 at 500 MHz.

	Hemiasterlin		Hemiasterlin A			Hemiasterlin B		
Carbon	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$	HMBC[a]	$\delta^{13}C$[b]	$\delta^{1}H$	HMBC[a]
1-N				10.93,s			10.88,s	
2	128.7	7.16,s	122.9	7.11,s	H1	122.9	7.06,s	
3	116.5		120.4		H2,5,6,14,15	119.0		H14,15
4	125.0		124.8		H1,2,8	124.8		H2.8
5	120.6	8.09,d,J=8 Hz	120.2	7.80,d,J=8 Hz		120.0	7.98,d,J=7.8 Hz	
6	121.1	7.07,t,J=8 Hz	120.7	7.06,t,J=8 Hz		120.4	7.05,t,J=7.8 Hz	
7	118.4	7.20,t,J=8 Hz	118.1	6.96,t,J=8 Hz	H8	117.8	6.95,t,J=7.8 Hz	H8
8	110.0	7.44,d,J=8 Hz	111.8	7.35,d,J=8 Hz		111.4	7.38,d,J=7.8 Hz	H7
9	137.7		137.3		H1,2,5,6	137.2		H2
10	37.5		37.9		H11,14,15	37.5		H14,15
11	67.5	4.44,d,J=6 Hz	71.7	3.47,s	H14,15,17	69.3	3.47,bs	
12	166.0		171.2		H11			
13	32.4	3.75,s						
14	27.0	1.41,s	27.5	1.41,s	H15	27.3	1.38,s	H15
15	22.5	1.38,s	23.2	1.37,s	H11,14	22.5	1.34,s	H14
16-N		7.38,bs						
17	33.4	2.24,s	35.2	1.92,s	H11	35.0	1.93,s	
18-N		8.87,s		7.84,bd,J=9 Hz				
19	56.2	4.84,d,J=8 Hz	53.8	4.79,d,J=9 Hz		53.8	4.58,t,J=8 Hz	H22,23
20	170.1		170.9		H19,30	171.0		H30
21	34.6		34.7		H19,22,23,24	30.0	2.11,m	H19,22
22	26.3	0.99,s	26.2	0.93,s	H19,23,24		0.84,d,J=6.3 Hz	
23	26.3	0.99,s	26.2	0.93,s	H19,22,24		0.89,d,J=6.3 Hz	
24	26.3	0.99,s	26.2	0.93,s	H19,22,23			
26	55.6	4.93,t,J=10 Hz	55.9	4.91,t,J=9 Hz	H30,32,33	55.8	4.87,t,J=10 Hz	H30,32,33
27	138.3	6.66,d,J=10 Hz	138.2	6.63,d,J=9 Hz	H26,34	137.7	6.63,d,J=8.8 Hz	H26,34
28	131.6		131.8		H26,34	131.5		H34
29	168.5		168.6		H27,34	168.5		H34
30	31.1	3.03,s	30.9	2.97,s	H26	30.0	2.98,s	
31	28.7	2.01,m	28.8	1.96,m	H26,32,33	28.7	2.08,m	H32,26
32	19.3	0.80,d,J=7 Hz	19.3	0.77,d,J=6.5 Hz	H33		0.74,d,J=6.1 Hz	
33	18.9	0.78,d,J=7 Hz	18.7	0.70,d,J=6.5 Hz	H32		0.80,d,J=6.1 Hz	
34	13.5	1.80,s	13.5	1.77,s	H27	13.0	1.75,s	H27

[a]Proton resonances that are correlated to the carbon resonance in the $\delta^{13}C$ column
[b]Obtained from HMQC and HMBC correlations

TABLE 4

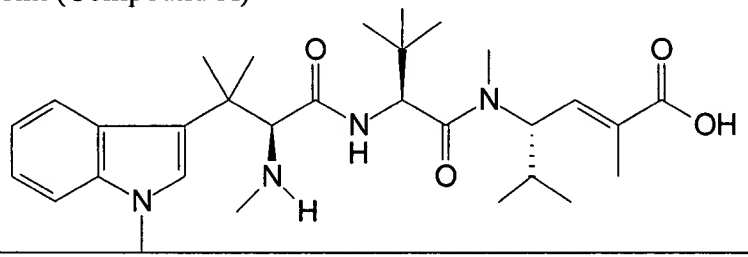
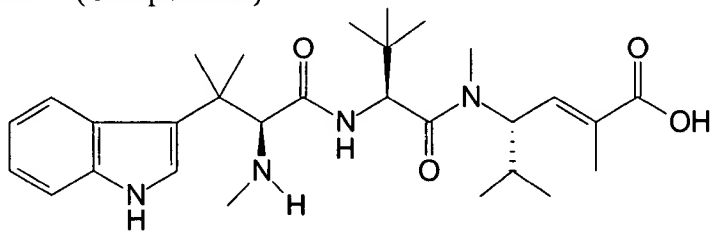
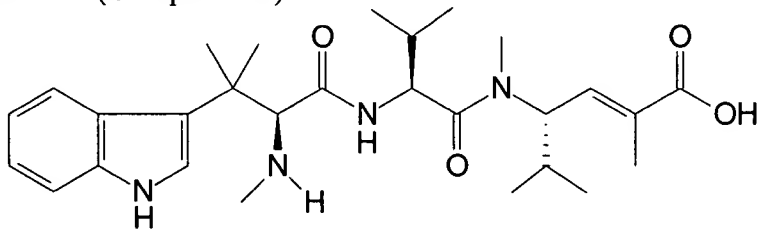
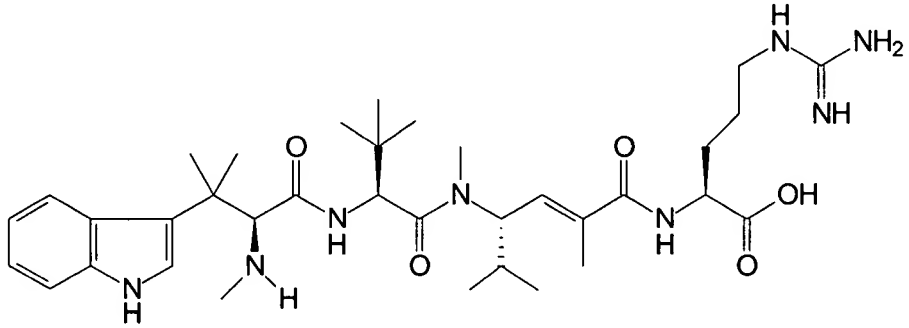
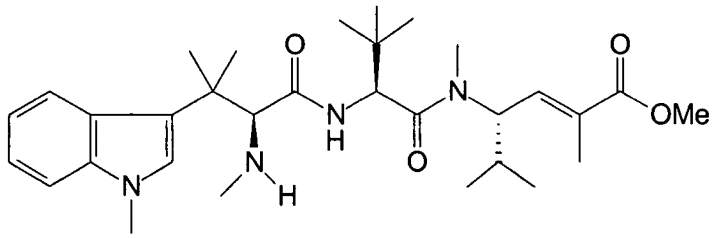
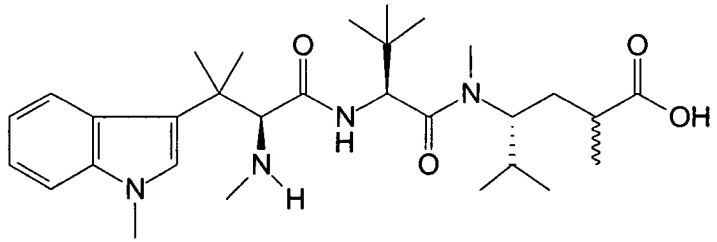
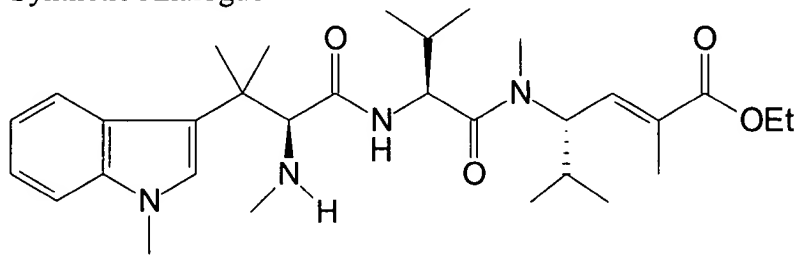
	IC_{50} Values (μg/ml)				
	P388	U373	HEY	MCF7	cell mitosis
Hemiasterlin (Compound A) 	4.57×10^{-5}	1.2×10^{-2}	1.4×10^{-3}	1.58×10^{-4}	1.58×10^{-4}
Hemiasterlin-A (Compound 2) 	1.71×10^{-6}	1.5×10^{-3}	7.6×10^{-3}	1.54×10^{-3}	1.02×10^{-3}
Hemiasterlin-B (Compound 3) 	7.0×10^{-3}		1.6×10^{-2}	1.5×10^{-2}	9.96×10^{-3}
Criamide-B 	7.3×10^{-3}	0.27	0.19	6.8	

TABLE 4 (Continued)

	IC_{50} Values (μg/ml)				
Geodiamolide G (Compound I)		7.7	8.6		
Hemiasterlin-OMe 				5.4×10^{-3}	2.16×10^{-4}
Dihydrohemiasterlin 					1.06×10^{-3}
Totally Synthetic Analogue 				0.1	